Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.2469

World J Gastroenterol 2009 May 28; 15(20): 2469-2471
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Walter Fries, MD, *Series Editor*

Combined therapeutic approach: Inflammatory bowel diseases and peripheral or axial arthritis

Fabiola Atzeni, Sandro Ardizzone, Luca Bertani, Marco Antivalle, Alberto Batticciotto, Piercarlo Sarzi-Puttini

Fabiola Atzeni, Luca Bertani, Marco Antivalle, Alberto Batticciotto, Piercarlo Sarzi-Puttini, Rheumatology Unit, L. Sacco University Hospital, Milan 20127, Italy
Sandro Ardizzone, Gastroenterology Unit, L. Sacco University Hospital, Milan 20127, Italy
Author contributions: Atzeni F wrote the paper and designed research; Ardizzone S wrote the paper; Bertani L and Antivalle M analyzed the data and performed research; Batticciotto A performed research; Sarzi-Puttini P revised the paper.
Correspondence to: Piercarlo Sarzi-Puttini, MD, Director, Rheumatology Unit, L. Sacco University Hospital, Milano 20127, Italy. atzenifabiola@hotmail.com
Telephone: +39-23-9042208 Fax: +39-23-9043454
Received: February 2, 2009 Revised: April 8, 2009
Accepted: April 15, 2009
Published online: May 28, 2009

Abstract

Inflammatory bowel diseases (IBDs), particularly Crohn's disease (CD) and ulcerative colitis (UC), are associated with a variety of extra-intestinal manifestations (EIMs). About 36% of IBD patients have at least one EIM, which most frequently affect the joints, skin, eyes and the biliary tract. The EIMs associated with IBD have a negative impact on patients with UC and CD, and the resolution of most of them parallels that of the active IBD in terms of timing and required therapy; however, the clinical course of EIMs such as axial arthritis, pyoderma gangrenosum, uveitis, and primary sclerosing cholangitis is independent of IBD activity. The peripheral and axial arthritis associated with IBD have traditionally been treated with simple analgesics, non-steroidal anti-inflammatory drugs, steroids, sulfasalazine, methotrexate, local steroid injections and physiotherapy, but the introduction of biological response modifiers such as tumor necrosis factor-α blockers, has led to further improvements.

Key words: Anti-tumor necrosis factor antagonists; Inflammatory bowel disease; Treatment; Arthropathies

Peer reviewer: Abraham R Eliakim, Professor, Gastroenterology, Rambam Medical Center, Technion School of Medicine, PO Box 9602, Haifa 31096, Israel

Atzeni F, Ardizzone S, Bertani L, Antivalle M, Batticciotto A, Sarzi-Puttini P. Combined therapeutic approach: Inflammatory bowel diseases and peripheral or axial arthritis. *World J Gastroenterol* 2009; 15(20): 2469-2471 Available from: URL: http://www.wjgnet.com/1007-9327/15/2469.asp DOI: http://dx.doi.org/10.3748/wjg.15.2469

INTRODUCTION

Inflammatory bowel diseases (IBD), particularly Crohn's disease (CD) and ulcerative colitis (UC), are associated with a variety of extra-intestinal manifestations (EIMs)[1]. About 36% of IBD patients have at least one EIM[2], and these have a negative impact on UC and CD patients. The most frequent EIMs affect the joints, skin, eyes and the biliary tract[3], but others give rise to small bowel dysfunctions (cholelithiasis, nephrolithiasis and obstructive uropathy) or are non-specific disorders (osteoporosis, hepatobiliary disease and amyloidosis)[1,2]. Although the association between EIMs and IBD has long been recognized, the underlying pathogenetic factors remain unclear. The reported incidence of peripheral and axial arthropathies ranges from 4% to 23%[4,5].

The Oxford group distinguished two types of peripheral arthropathy on the basis of their articular involvement[4]: (1) Type I is a large joint pauci-articular arthropathy that mainly affects the ankles, knees, hips, wrists, elbows and shoulders; is usually acute and self-limiting; occurs at times of IBD activity; and leaves no permanent joint damage. (2) Type II is a polyarticular arthropathy that mainly affects the small joints of both hands symmetrically; is characterised by pain that usually persists for months or years; and is largely independent of IBD activity.

Axial arthritis includes sacroiliitis and ankylosing spondylitis (AS)[5]: (1) Sacroiilitis may be asymptomatic or symptomatic[6]; asymptomatic sacroiilitis is common and up to 50% of CD patients show abnormal radiographic findings; symptomatic sacroiliitis is characterised by pain in the pelvis after rest, which improves with movement, and discomfort in the sacroiliac joints during bilateral pressure on the pelvic brim. (2) AS is characterised by persistent low back pain beginning before the age

of 30 years, and its clinical diagnosis is supported by characteristic radiological changes for which magnetic resonance imaging is the diagnostic tool of choice[7,8]. Although HLA B-27 is over-represented in IBD-related axial arthritis, it is of no diagnostic value[9].

THERAPEUTIC APPROACHES TO IBD AND ARTHROPATHIES

The treatment of IBD-associated arthropathies is almost entirely based on extrapolations from other forms of arthritis.

In the case of type I peripheral arthritis, treatment should concentrate on the active disease and include steroids, immunomodulators and anti-tumor necrosis factor-α (TNF-α)[10-12]; however, all forms of IBD-related arthritis seem to be treated with sulfasalazine (SSZ) despite the lack of supportive evidence[13]. The symptoms can be relieved using simple analgesics, rest and physiotherapy. Non-steroidal anti-inflammatory drugs may aggravate the underlying colitis[14], but the findings of a randomised study regarding the safety of celecoxib[15] indicate that its short-term use (< 2 wk) does not exacerbate colitis. A local steroid injection into the affected joints provides rapid but only temporary relief.

The treatment of AS should include intensive physiotherapy, together with the administration of disease-modifying drugs such as SSZ and methotrexate. However, since TNF-α has been shown to play a key role in the pathogenesis of AS and IBD, the treatment of this manifestation has changed[16].

The advent of biological response modifiers such as TNF-α blockers has improved the treatment of IBD and its associated peripheral and axial arthritides, and their safety and efficacy have been clearly established in the case of AS-related peripheral arthritis. IBD patients failing on immunomodulation therapy used to be recommended surgery, but are now treated with biological agents.

Table 1 lists the currently used treatments for IBD-related arthropathies.

Table 1 Therapy of spondyloarthropathies

Therapy	
Standard initial therapy	NSAIDs and anti-COX-2
	Physical activity
	Local steroids
Second line therapy	Sulfasalazine
	Methotrexate
	Gold
	Others (penicillamine, *etc*)
Biological therapies (TNFα-blockers)	Infliximab
	Etanercept
	Onercept
	Adalimumab
	Thalidomide

Anti-TNF antagonists

Infliximab is a chimeric IgG1 monoclonal antibody to TNF and represents a significant advance in the treatment of IBD with or without associated arthropathies[17]. There are anecdotal accounts of infliximab rapidly improving peripheral arthritis in IBD patients. Ellman *et al*[18] have reported the findings of an open-label study in which four patients with treatment-refractory peripheral arthritis responded to treatment with infliximab 5 mg/kg and, subsequently, a large-scale prospective, open-label trial demonstrated an improvement in peripheral arthritis in IBD patients who had previously been refractory to corticosteroids, 6-mercaptopurine, azathioprine or methotrexate[19]. Another small open-label study documented an improvement in the arthralgias of seven out of 11 IBD patients after a single infusion of infliximab 5 mg/kg[20].

On the basis of the available data, it seems that most IBD patients with active intestinal inflammation and concurrent peripheral arthritis are likely to experience an improvement in their joint symptoms upon receiving infliximab.

Adalimumab is a subcutaneously self-administered fully human monoclonal antibody against TNF-α that is efficacious in inducing and maintaining remission in patients with moderate-to-severe CD[21], but there are no published data concerning its efficacy in patients with concomitant IBD and arthritis.

Infliximab, etanercept and adalimumab have all been found to have positive short- and long-term effects on disease signs and symptoms in AS patients[22,23]. Braun *et al*[24] analysed the data from nine trials of anti-TNF agents (seven placebo-controlled and two open-label studies) and found that the treatment is efficacious in treating AS and IBD, and that the onset and flare of IBD are infrequent events in AS patients receiving anti-TNF therapy. Infliximab (but not etanercept) largely prevents IBD and AS activity but more data are required in the case of adalimumab.

The efficacy of adalimumab in the treatment of AS is mainly supported by the findings of the recent multicentre, randomized, double-blind and placebo-controlled trial conducted by van der Heijde *et al*[25] who observed that the response of most of the patients treated with adalimumab was better than that observed in the patients treated with placebo.

No published studies have yet addressed the effect of switching from infliximab to adalimumab in patients with CD-related spondyloarthropathy. We have recently evaluated the clinical response to adalimumab of 19 CD patients with associated spondyloarthritis who discontinued infliximab because of intolerance or loss of efficacy, and found that it successfully controlled both articular and intestinal disease activity[26].

In conclusion, about 36% of IBD patients have at least one EIM, especially articular involvement, and the introduction of anti-TNF therapy has improved the treatment of both. In particular, the subgroup of Crohn's disease patients with arthritic problems could be the one in which anti-TNF agents are most indicated.

REFERENCES

1 **Ardizzone S**, Puttini PS, Cassinotti A, Porro GB. Extraintestinal manifestations of inflammatory bowel disease. *Dig Liver Dis* 2008; **40** Suppl 2: S253-S259
2 **Su CG**, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 307-327
3 **Urlep D**, Mamula P, Baldassano R. Extraintestinal manifestations of inflammatory bowel disease. *Minerva Gastroenterol Dietol* 2005; **51**: 147-163
4 **Orchard TR**, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 1998; **42**: 387-391
5 **Fornaciari G**, Salvarani C, Beltrami M, Macchioni P, Stockbrügger RW, Russel MG. Muscoloskeletal manifestations in inflammatory bowel disease. *Can J Gastroenterol* 2001; **15**: 399-403
6 **Bjarnason I**, Helgason KO, Geirsson AJ, Sigthorsson G, Reynisdottir I, Gudbjartsson D, Einarsdottir AS, Sherwood R, Kristjansson K, Kjartansson O, Thjodleifsson B. Subclinical intestinal inflammation and sacroiliac changes in relatives of patients with ankylosing spondylitis. *Gastroenterology* 2003; **125**: 1598-1605
7 **Heuft-Dorenbosch L**, Landewé R, Weijers R, Wanders A, Houben H, van der Linden S, van der Heijde D. Combining information obtained from magnetic resonance imaging and conventional radiographs to detect sacroiliitis in patients with recent onset inflammatory back pain. *Ann Rheum Dis* 2006; **65**: 804-808
8 **Zochling J**, Baraliakos X, Hermann KG, Braun J. Magnetic resonance imaging in ankylosing spondylitis. *Curr Opin Rheumatol* 2007; **19**: 346-352
9 **Steer S**, Jones H, Hibbert J, Kondeatis E, Vaughan R, Sanderson J, Gibson T. Low back pain, sacroiliitis, and the relationship with HLA-B27 in Crohn's disease. *J Rheumatol* 2003; **30**: 518-522
10 **Dale J**, Alcorn N, Capell H, Madhok R. Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. *Nat Clin Pract Rheumatol* 2007; **3**: 450-458; quiz, following 478
11 **Akkoc N**, van der Linden S, Khan MA. Ankylosing spondylitis and symptom-modifying vs disease-modifying therapy. *Best Pract Res Clin Rheumatol* 2006; **20**: 539-557
12 **Caporali R**, Pallavicini FB, Filippini M, Gorla R, Marchesoni A, Favalli EG, Sarzi-Puttini P, Atzeni F, Montecucco C. Treatment of rheumatoid arthritis with anti-TNF-alpha agents: a reappraisal. *Autoimmun Rev* 2009; **8**: 274-280
13 **Chen J**, Liu C. Sulfasalazine for ankylosing spondylitis. *Cochrane Database Syst Rev* 2005: CD004800
14 **Takeuchi K**, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, Bjornsson E, Bjarnason I. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006; **4**: 196-202
15 **Sandborn WJ**, Stenson WF, Brynskov J, Lorenz RG, Steidle GM, Robbins JL, Kent JD, Bloom BJ. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. *Clin Gastroenterol Hepatol* 2006; **4**: 203-211
16 **Zochling J**, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr, Dijkmans B, Dougados M, Géher P, Inman RD, Khan MA, Kvien TK, Leirisalo-Repo M, Olivieri I, Pavelka K, Sieper J, Stucki G, Sturrock RD, van der Linden S, Wendling D, Böhm H, van Royen BJ, Braun J. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; **65**: 442-452
17 **Barrie A**, Regueiro M. Biologic therapy in the management of extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 1424-1429
18 **Ellman MH**, Hanauer S, Sitrin M, Cohen R. Crohn's disease arthritis treated with infliximab: an open trial in four patients. *J Clin Rheumatol* 2001; **7**: 67-71
19 **Herfarth H**, Obermeier F, Andus T, Rogler G, Nikolaus S, Kuehbacher T, Schreiber S. Improvement of arthritis and arthralgia after treatment with infliximab (Remicade) in a German prospective, open-label, multicenter trial in refractory Crohn's disease. *Am J Gastroenterol* 2002; **97**: 2688-2690
20 **Kaufman I**, Caspi D, Yeshurun D, Dotan I, Yaron M, Elkayam O. The effect of infliximab on extraintestinal manifestations of Crohn's disease. *Rheumatol Int* 2005; **25**: 406-410
21 **Devlin SM**, Panaccione R. Adalimumab for the treatment of Crohn's disease. *Expert Opin Biol Ther* 2008; **8**: 1011-1019
22 **Generini S**, Giacomelli R, Fedi R, Fulminis A, Pignone A, Frieri G, Del Rosso A, Viscido A, Galletti B, Fazzi M, Tonelli F, Matucci-Cerinic M. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. *Ann Rheum Dis* 2004; **63**: 1664-1669
23 **Maksymowych WP**. Update on the treatment of ankylosing spondylitis. *Ther Clin Risk Manag* 2007; **3**: 1125-1133
24 **Braun J**, Baraliakos X, Listing J, Davis J, van der Heijde D, Haibel H, Rudwaleit M, Sieper J. Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor alpha agents. *Arthritis Rheum* 2007; **57**: 639-647
25 **van der Heijde D**, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, Dougados M, Reveille JD, Wong RL, Kupper H, Davis JC Jr. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; **54**: 2136-2146
26 **Antivalle M**, Bertani L, Atzeni F, Battellino M, Batticciotto A, Montalbano F, Mutti A, Sarzi-Puttini P. Disease activity and quality of life in Crohn's-associated spondyloarthropathy after switching from infliximab to adalimumab. *Clin Exp Rheum* 2008; **26**: 746

S- Editor Tian L **L- Editor** Logan S **E- Editor** Zheng XM